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Investigation of S100A12 levels in children with community-acquired pneumonia

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Abstract

Aim: Community-acquired pneumonia is an important cause of morbidity and mortality in the world. Prompt diagnosis and appropriate treatment are essential. The efficiency of existing biomarkers alone is not sufficient for diagnosis, so the search for new biomarkers continues. S100A12 is involved in innate immune responses against microorganisms and parasites. The aim of this study is to investigate the relationship between S100A12 levels and routine inflammation markers and disease activity in children diagnosed with community-acquired pneumonia.

Material and Methods: Serum S100A12 (by ELISA method) and C-reactive protein (CRP; by immunonephelometric method) levels were measured for both patients (n=60) and a control group (n=50).

Results: Levels of CRP and S100A12 were found to be significantly higher in patients with community-acquired pneumonia compared to the control group. CRP and S100A12 levels were also significantly higher in the subgroup of patients with severe disease activity.

Discussion: S100A12 levels were found to be significantly higher in children with community-acquired pneumonia in our study, and a significant relationship was found between the severity of the disease and S100A12. These findings indicate that S100A12 may be a new marker that has a place in prognostic evaluation, in addition to its similar properties to other inflammation markers in the evaluation of community-acquired pneumonia.

Keywords

S100A12, C-Reactive Protein, Community-Acquired Pneumonia

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Introduction

Clinical and radiological findings in community-acquired pneumonia (CAP) patients are not reliable in determining the etiological factor. Among the general parameters associated with the presence of infection, white blood cell (WBC) count, neutrophil count, erythrocyte sedimentation rate, C-reactive protein (CRP), and procalcitonin are commonly used markers [1]. However, to date, the efficiency of these biomarkers alone is not high enough and the search for new biomarkers continues.

S100A12 is thought to be an important marker for many inflammatory diseases in humans [2]. However, there is no study in the literature investigating S100A12 levels in children with CAP. Only Hou et al. examined S100A12 levels in adults with bacterial pneumonia [3]. Considering the results in diseases with inflammation, CAP may be suggested as a candidate for application of this biomarker in diagnosis and monitoring.

Our aim is to evaluate levels of S100A12 in children diagnosed with CAP and to investigate its relationship with routine inflammation markers and disease activity.

Material and Methods

Fifty patients who applied to the University of Health Sciences Mehmet Akif İnan Training and Research Hospital's Pediatric Outpatient Clinic and were diagnosed with CAP were included in this study. The control group comprised 50 healthy children. CAP patients were divided into subgroups of patients with mild to moderate pneumonia (n=31) and severe pneumonia (n=29) according to disease activity [4].

Serum samples were obtained by taking 2 mL of blood and were stored in a freezer at -86 °C. The S100A12 levels of these samples were studied by ELISA method (Bioassay Technology Laboratory Human S100 A12 ELISA Kit No. E3074) for both patients and the control group. Serum CRP levels were also measured with a Cobas c501 biochemistry device (Roche Diagnostics, Turkey) by immunonephelometric method. Blood was taken into EDTA tubes for complete blood count analysis performed with a Penta DX-Nexus device.

Statistics

Evaluation of the data was conducted using SPSS 21.00 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used.

Results

Maternal age, CRP, and S100A12 were found to be significantly higher in CAP patients compared to the control group. WBC and neutrophil counts were also significantly higher in CAP patients compared to the control group (Table 1). CRP and S100A12 levels were significantly higher in the subgroup of patients with severe disease activity (Table 2). As a result of the correlation analysis, a negative, weak relationship was found between CRP and S100A12, while a positive, weak, and significant relationship was found between WBC count and S100A12 (Table 3). As a result of the analysis performed to determine the correlation between S100A12 and the considered variables, no significant relationship was found in the control group (Table 3). In stepwise regression analysis, significant relationships were found between S100A12 and CRP (p=0.003) and age (p=0.046). Receiver operating characteristic (ROC) curve analysis was performed for CRP, S100A12, neutrophils, WBC count, and

Table 1. Statistical evaluation of the parameters examined between pediatric patients with CAP and the control group

Parameters	CAP	Control	p
Age (months)	67.1±47.1	85.9±38.5	0.10
Gestational age at birth (weeks)	38.4±3.3	39.2±1.4	0.93
Mother's age (years)	31.2±5.6	36.3±5.8	0.00
CRP (mg/dL)	21.3 (0.2-268)	2.3 (0.5-4.6)	0.00
Hb (g/dL)	12.8±1.4	12.5±0.9	0.14
Hct (%)	38.0±3.7	37.4±2.5	0.40
WBC (×103/μL)	9,6 (1.4-28.5)	6.9 (3.8-11.2)	0.01
Neutrophils (×103/μL)	5.3 (0.8-22.7)	32.3 (1.3-6.7)	0.03
Lymphocytes (×103/μL)	3,4 (0.7-17.6)	2.9 (1.6-5.3)	0.66
Neutrophil/lymphocyte ratio	2.3 (0.14-14.7)	1.2 (0.5-2.6)	0.22
PLT (×103/μL)	354.5±901.0	324.3±55.9	0.04
S100A12 (ng/mL)	1419.3 (686.2-2093.7)	1101.3 (677.6-1348)	0.03

CRP: C-reactive protein; Hb: Hemoglobin, Hct: Hematocrit; WBC: White blood cell count, PLT: Platelet count.

Table 2. Comparison of pediatric patients with CAP according to disease activity

Parameters	Mild/moderate	Severe	p
Age (months)	69.2±48.1	64.8±47.6	0.72
Gestational age at birth (weeks)	37.6±4.2	39.4±1.4	0.24
Birth weight (kg)	3.0±0.8	3.4±0.8	0.09
Mother's age (years)	30.5±5.5	32.0±5.7	0.32
Breast milk intake (months)	16.2±11.7	12.0±8.2	0.12
Number living in house	4.4±1.3	4.5±1.6	0.80
Duration of symptoms (days)	10.6±16.7	14.7±18.6	0.38
CRP (mg/dL)	9.1 (0.2-58.1)	34.4 (1.22-268)	0.01
Hb (g/dL)	13.0±1.5	12.6±1.3	0.28
Hct (%)	38.3±3.9	37.6±3.6	0.66
WBC (×103/μL)	8.6 (1.5-28.5)	10.7 (4.7-26.6)	0.09
Neutrophils (×103/μL)	4.5 (1.0-22.7)	5.7 (0.8-16.2)	0.18
Lymphocytes (×103/μL)	3.1 (1.4-8.6)	3.8 (0.7-17.6)	0.27
Neutrophil/lymphocyte ratio	1.91(0.1-7.6)	2.81 (0.25-14.71)	0.95
PLT (×103/μL)	358.3±79.5	350.4±101.6	0.74
S100A12 (ng/mL)	1248 (686.2-2093.8)	1566.2 (823.9-1991.2)	0.01

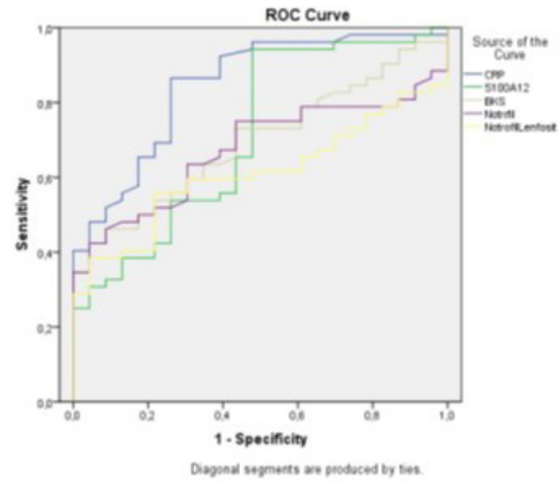

Figure 1. ROC curve of CRP, S100A12, WBC count, neutrophil count, and neutrophil/lymphocyte values

Table 3. Correlation coefficients (r) between parameters examined in the pediatric patient group with CAP and the control group

	S100A12	
	CAP	Control group
Age (months)	-0.376	-0.064
Gestational age at birth (weeks)	0.134	0.158
Birth weight (kg)	0.127	-0.021
Mother's age (years)	-0.055	0.340
CRP (mg/dL)	-0.281	-0.244
Hb (g/dL)	-0.222	-0.023
Hct (%)	-0.235	-0.044
WBC (×103/μL)	0.301	0.061
Neutrophils (×103/μL)	0.218	0.152
Lymphocytes (×103/μL)	0.068	-0.113
Neutrophil/lymphocyte ratio	0.225	0.328
PLT (×103/μL)	0.144	-0.323
Disease activity	0.374	-
Breast milk intake (months)	-0.182	0.338

neutrophil/lymphocyte ratio in the prediction of the efficacy of these biomarkers in patients with pneumonia. As a result of this analysis, CRP (AUC=0.84, 95% CI=0.752-0.939), S100A12 (AUC=0.71, 95% CI=0.58-0.84), neutrophils (AUC=0.67, 95% CI=0.55-0.79), WBC count (AUC=0.696, 95% CI=0.579-0.813), and neutrophil/lymphocyte ratio (AUC=0.61, 95% CI=0.48-0.73) were found to have diagnostic value (Figure 1). However, the AUC values for neutrophils, WBC count, and neutrophil/lymphocyte ratio were found to be below the acceptance value of 0.70 for areas under the ROC curve.

Discussion

In our study, the CRP values and WBC and neutrophil counts of the patients with CAP were found to be significantly higher than those of the control group. These results confirm that acute phase response is increased in patients with CAP. The neutrophil count was similarly found to be significantly higher in other research [5], although Chalupa et al. [6] could not find a significant difference in neutrophil levels in 21 adult patients with bacterial CAP compared to a control group. At the same time, CRP values are found to be higher in cases of invasive acute bacterial infections but lower in viral infections [7]. The analysis of CRP and WBC count is cheap, simple, and widely used, but CRP is not specific in patients with CAP because it is a general acute phase protein [8].

In our study, the S100A12 levels of CAP patients were found to be significantly higher than those of the control group. There is no other study examining S100A12 levels in childhood cases of CAP in the literature. However, Hou et al. [3] found increased S100A12 levels in 12 of 46 adult patients with bacterial pneumonia. Again supporting our findings, Achouiti et al. [9] found that S100A12 levels were significantly higher among 29 severe sepsis pneumonia patients compared to 31 healthy controls. High concentrations of S100A12 were also found in bronchial alveolar lavage fluid in cases of acute lung inflammation characterized by diffuse alveolar damage [10]. Since S100A12 is a small protein weighing 9-14 kDa, it can easily diffuse into the blood [11].

In our study, S100A12 levels were significantly higher in patients with severe pneumonia than patients with mild to moderate pneumonia. No study in the literature to date has investigated the relationship between S100A12 levels and disease activity in patients with pneumonia. However, results showing that S100A12 is associated with disease activity in other diseases with chronic inflammation have been reported [12].

In our study, only CRP levels in children with severe CAP were found to be significantly higher compared to the group with mild to moderate CAP. Although WBC count, neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio were high in patients with severe CAP, these results did not reach statistical significance. In other studies, CRP levels were found to be significantly higher in children with severe CAP, similar to our findings [13].

In our group of patients with CAP, positive correlations were found between serum S100A12 and CRP and WBC count. Supporting our findings, Heu et al. found positive correlations between S100A12 and WBC count and CRP in patients with bacterial pneumonia [3]. High correlations of traditional inflammatory markers with S100A12 levels clearly reveal that S100A12 can be used as a biomarker. This also suggests that the level of S100A12 may reflect the severity and presence of inflammation in CAP.

In our study, positive correlations were found between S100A12 and CRP and disease activity. However, no correlation was found between WBC count and disease activity. Contrary to these findings, Kim et al. [14] found low correlations between CRP and WBC count and CAP severity in their study with 155 elderly CAP patients. Liu et al. [15] found only a positive correlation between disease activity and CRP. Kao et al. [5] did not show a significant correlation between disease activity and CRP in their study with 61 CAP patients, similarly to the findings of Hedlund and Hansson [16] in a study conducted with 96 CAP patients. All these findings demonstrate that the disease activity-related results of CRP and WBC are contradictory and do not reflect the severity of the disease alone.

The results of the linear regression analysis performed to determine the independent factors affecting S100A12 levels as a continuous variable in patients with CAP are shown in Table 1. In this model, age and CRP levels were found to be independent factors affecting S100A12 levels. This relationship between S100A12 and CRP is an important result that supports the relationship of S100A12 with inflammation in patients with CAP.

The possibility of the serum S100A12 level of a randomly selected patient among individuals with CAP being higher than the serum S100A12 level of a randomly selected individual from among the controls without CAP was investigated by ROC analysis in our study. The area under the ROC curve showed that our results, which were 0.846 (p=0.000) for CRP and 0.713 (p=0.003) for S100A12, were acceptable. Reviewing the literature, AUC values of >0.70 for CRP were found to be significant in studies of patients with CAP [13]. These results support the usability of S100A12 in the diagnosis of CAP, but also show that its effectiveness is lower than that of CRP. However, the measurement of S100A12 can be especially useful in patients with negative CRP results in the first 12 hours

or in the presence of other inflammatory conditions that cause increases in CRP.

WBC counts and CRP values are often obtained in hospitalized children with pneumonia. However, the potential role of WBC count and CRP in predicting disease courses and clinical outcomes remains unclear. Although the results of various pneumonia studies indicate that CRP values are useful in predicting clinical outcomes, it has also been reported that acute phase inflammation is a non-specific marker [17]. As a result, new markers are being investigated due to the lack of available markers in the diagnosis and treatment of this disease. We therefore tried to show that S100A12, a new marker in the diagnosis of inflammatory diseases, can be used in the diagnosis of patients with CAP, and we also sought to explain its relationship with CRP, an inflammatory marker.

As a result, S100A12 levels were found to be significantly higher in children with CAP in our study, and a significant relationship was found between the severity of the disease and S100A12 levels. These findings indicate that S100A12 may be a new marker that has a place in prognostic evaluation, in addition to having properties similar to those of other inflammation markers in the evaluation of CAP. However, we are of the opinion that the course and prognostic value of S100A12 in cases of CAP, a disease with highly variable pathogenesis and prognosis, should be studied in larger series of patients with similar phenotypes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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References

1. Derneği TT, Kongresi YJTTJ. Erişkinlerde toplumda gelişen pnömoni tanı ve tedavi uzlaşı raporu. Klimik Dergisi. 2009;10(Suppl 9):1-12.

2. Day A, Ehn M, Gearry R, Lemberg D, Leach SJDm. Fecal S100A12 in healthy infants and children. Hindawi. 2013;35(5):295-9.

3. Hou F, Wang L, Wang H, Gu J, Li M, Zhang J, et al. Elevated gene expression of S100A12 is correlated with the predominant clinical inflammatory factors in patients with bacterial pneumonia. Mol Medicine Reports. 2015;11(6):4345-52.

4. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011;66(Suppl 2):ii1-ii23.

5. Kao S-J, Yang H-W, Tsao S-M, Cheng C-W, Bien M-Y, Yu M-C, et al. Plasma long pentraxin 3 (PTX3) concentration is a novel marker of disease activity in patients with community-acquired pneumonia. Clinical Chemistry and Laboratory Medicine. 2013;51(4):907-13.

6. Chalupa P, Beran O, Herwald H, Kaspříková N, Holub MJI. Evaluation of potential biomarkers for the discrimination of bacterial and viral infections. Infection.2011;39(5):411-7.

7. Baumann H, Gauldie JJIt. The acute phase response. Immunology today. 1994;15(2):74-80.

8. Justo D, Lachmi S, Saar N, Joffe E, Atzmony L, Mashav N, et al. C-reactive protein velocity following antibiotics in patients with chronic obstructive pulmonary disease exacerbation and community acquired pneumonia. European Journal of Internal Medicine. 2009;20(5):518-21.

9. Achouiti A, Föll D, Vogl T, van Till JW, Laterre P-F, Dugernier T, et al. S100A12 and soluble receptor for advanced glycation end products levels during human severe sepsis. Shock. 2013;40(3):188-94.

10. Wittkowski H, Sturrock A, van Zoelen MA, Viemann D, van der Poll T, Hoidal JR, et al. Neutrophil-derived S100A12 in acute lung injury and respiratory distress syndrome. Critical Care Med. 2007;35(5):1369-75.

11. Pietzsch J, Hoppmann SJAa. Human S100A12: a novel key player in inflammation? Amino Acids. 2009;36(3):381-9.

12. Cockayne DA, Cheng DT, Waschki B, Sridhar S, Ravindran P, Hilton H, et al. Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity. PloS one. 2012;7(6):e38629.

13. Agapakis DI, Tsantilas D, Psarris P, Massa EV, Kotsaftis P, Tziomalos K, et al. Coagulation and inflammation biomarkers may help predict the severity of community-acquired pneumonia. Respirology. 2010;15(5):796-803.

14. Kim JH, Seo JW, Mok JH, Kim MH, Cho WH, Lee K, et al. Usefulness of plasma procalcitonin to predict severity in elderly patients with community-acquired pneumonia. Tuberc Respir Dis. 2013;74(5):207.

15. Garcia-Laorden MI, Sole-Violan J, Rodriguez de Castro F, Aspa J, Briones ML, Garcia-Saavedra A, Rajas O, Blanquer J, et al. Mannose-binding lectin and mannose-binding lectin-associated serine protease 2 in susceptibility, severity, and outcome of pneumonia in adults. J Allergy Clin Immunol. 2008;122(2):368-74, 374.e1-2.

16. Hedlund J, Hansson L-OJI. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. Infection. 2000;28(2):68-73.

17. Bruns AH, Oosterheert JJ, Hak E, Hoepelman AIJERJ. Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. Rev Port Pneumol. 2008;32(3):726-32.

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